Supplementary

Contents

1. Yang et al., 2012

Maternal age less than 35 years, normal karyotype, no prior miscarriages. Day 5 trophectoderm biopsy and aCGH using 24Sure (BlueGnome, Cambridge, UK). The primary outcome measure was ongoing clinical pregnancy (>=20wks) following a fresh single embryo transfer on day 6 of an embryo with an euploid test result and compared to morphological assessment only. The ongoing pregnancy rates (OPR) were 69.1% (38/55) and 41.7% (20/48) for the test and control groups respectively. The corresponding clinical miscarriage rates (CMR) were 2.6% (1/38) and 9.1% (2/22) respectively.

The following contingency tables were constructed:

Table 1.

Yang et al.		Embryo outcome		
Age: <35 y		OP +ve	OP -ve	Total
Test result	Normal	38047	17012	55059
	Abnormal	3620	41321	44941
	Total	41667	58333	100000

With a prevalence of non-viable embryos of 58.3% (58,333 / 100,000), the predictive value was estimated to be 91.9% (41,321 / 44,941) for an abnormal result and no ongoing pregnancy, and 69.1% (38,047 / 55,059) for a normal result and an ongoing pregnancy.

Table 2.

Yang et al.			
Age: <35 y	No test	PGT-A	RR
Embryos transfered	100000	55059	0.551
Ongoing clinical pregnancies	41667	38047	0.913
Per transfer	41.7%	69.1%	1.658

The PGT-A ongoing pregnancy rate per embryo transferred was estimated to be superior (69.1% vs 41.7%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo; however, with 8.7% [(41,667 - 38,047) / 41,667) fewer ongoing pregnancies overall due to the exclusion of viable embryos with false positive test results.

Table 3. Model outcome measures

Couples	100,000	Fresh + warmed embryo transfer strategy

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Ongoing pregnancies	Clinical miscarriages	Transfers	First attempt ongoing preg.	Ongoing pregnancies	Clinical miscarriages	Transfers	First attempt ongoing preg.
1	41,667	4,167	100,000	41,667	38,047	1,028	55,059	38,047
2	64,514	6,451	154,833	41,667	61,230	1,655	88,608	55,146
3	78,413	7,841	188,190	41,667	75,557	2,042	109,341	62,830
4	86,868	8,687	208,481	41,667	84,506	2,284	122,291	66,283
5	92,011	9,201	220,826	41,667	90,140	2,437	130,445	67,835
6	95,140	9,514	228,335	41,667	93,708	2,533	135,608	68,533
7	97,044	9,704	232,903	41,667	95,977	2,594	138,892	68,846
8	98,202	9,820	235,682	41,667	97,424	2,634	140,986	68,987
9	98,906	9,891	237,372	41,667	98,349	2,659	142,324	69,051
10	99,334	9,934	238,401	41,667	98,941	2,675	143,181	69,079

Adapted with permission from Scriven (2016).

For 100,000 women with 8 morphologically transferable embryos (the average from the Yang et al. 2012 trial report) and considering only up to one transfer attempt, the numbers of women with a live birth event are 68,987 with PGT-A and 41,667 without testing (difference 65.6%). Following a full cycle for 100,000 women there are 98,202 (98.2%) vs 97,424 (97.4%) live births (difference -0.8%). There are 2,634 vs 9,820 miscarriages (difference -73.2%) and 140,986 vs 235,682 transfers (difference -40.2%).

Given 8 embryos suitable for transfer or testing, approximately 1 in 9 women [100,000 / (9,820 – 2,634)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with an ongoing pregnancy of around 1 in 126 [98,202 / (98,202 – 97,424)].

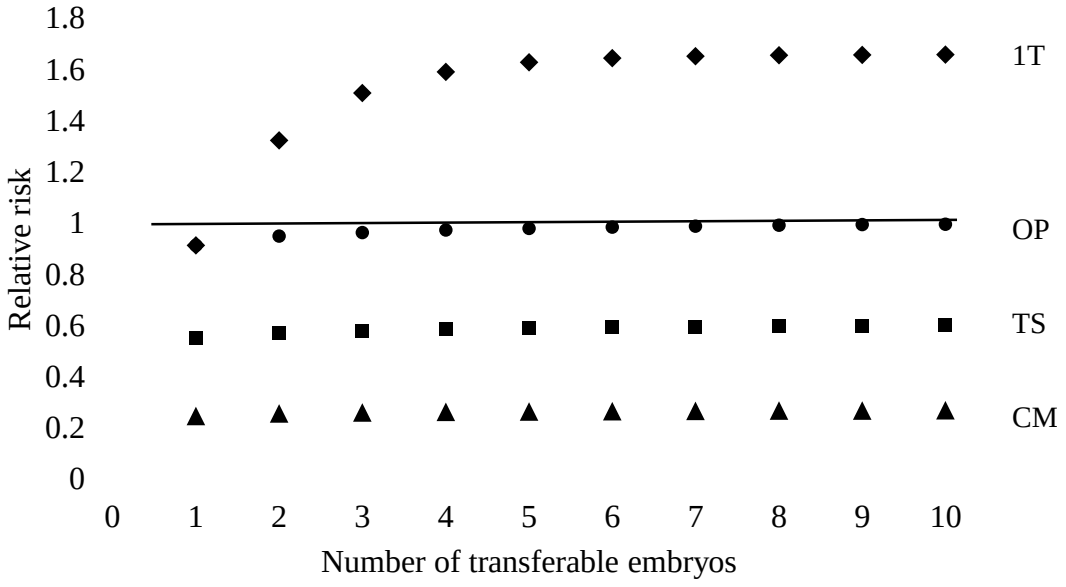

Fig.1. Based on Yang et al., 2012. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Ongoing pregnancy considering only up to 1 transfer attempt (1T). Ongoing pregnancies (OP), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle.

2. Rubio et al., 2017; Verpoest et al., 2018

Two PGT-A randomised controlled trials have considered cumulative live birth rate (Rubio et al., 2017 [NCT01571076]; Verpoest et al., 2018 [NCT01532284 the ESTEEM trial]). Neither study used blastocyst biopsy (cleavage-stage and polar body respectively) and both employed 24Sure aCGH. More than 1 embryo was transferred when available and more embryos were available for transfer in the control group and multiple embryo transfer was more often performed. It could be argued that this may have introduced a bias and favoured the control group by increasing the pregnancies in the fresh transfer cycle, while on the other hand it may have been a disadvantage to the control group, because single embryo transfer would have allowed for good quality embryos to be cryopreserved and transferred later only to add to the cumulative birth rate. Cumulative outcome data were limited to 6 months and 1 year respectively, which may have introduced a negative bias to the control group. The data were extrapolated to simulate transfer of every morphologically transferable embryo from a first full cycle one at a time until a first live birth event was achieved or no more embryos were available without discontinuing treatment.

The following contingency tables were constructed:

Table 4.

Rubio et al. 2017		Embryo outcome		
Age: 38 - 41 y		LB +ve	LB -ve	Total
Test result	Normal	10708	10707	21415
	Abnormal	6459	72126	78585
	Total	17167	82833	100000

With a prevalence of non-viable embryos of 82.8% (82,833 / 100,000), the predictive value was estimated to be 91.8% (72,126 / 78,585) for an abnormal result and no live birth, and 50% (10,708 / 21,415) for a normal result and a live birth.

Table 5.

Rubio et al. 2017			
Age: 38 - 41 y	No test	PGT-A	RR
Embryos transferred	100000	21415	0.214
Live births	17167	10708	0.624
Per transfer	17.2%	50.0%	2.913

The PGT-A live birth rate per embryo transferred was estimated to be superior (50.0% vs 17.2%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo; however, with 37.6% [(17,167 - 10,708) / 17,167) fewer live births overall due to the exclusion of viable embryos with false positive test results.

Table 6.

Verpoest et al. 2018		Embryo outcome		
Age: 36 - 40 y		LB +ve	LB -ve	Total
Test result	Normal	8073	27192	35265
	Abnormal	4882	59853	64735
	Total	12955	87045	100000

With a prevalence of non-viable embryos of 87.0% (87,045 / 100,000), the predictive value was estimated to be 92.5% (59,853 / 64,735) for an abnormal result and no live birth, and 22.9% (8,073 / 35,265) for a normal result and a live birth.

Table 7.

Verpoest et al. 2018			
Age: 36 - 40 y	No test	PGT-A	RR
Embryos transferred	100000	35265	0.353
Live births	12955	8073	0.623
Per transfer	13.0%	22.9%	1.767

The PGT-A live birth rate per embryo transferred was estimated to be superior (22.9% vs 13.0%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo; however, with 37.7% [(12,955 - 8,073) / 12,955) fewer live births overall due to the exclusion of viable embryos with false positive test results.

The clinical miscarriage rates for the control and study groups were estimated to be 36.1% (22/61) vs 6.3% (3/48) (Rubio et al. 2017) and 37.5% (27/72) vs 21.9% (14/64) (Verpoest et al. 2018). Considering only up to one transfer attempt, when more than one morphologically transferable embryo is available there are more live birth events with PGT-A, which indicates that PGT-A is more effective than a conventional morphological assessment alone to select a viable embryo. Including the transfer of all available cryopreserved embryos, the cumulative live birth rate is inferior with PGT-A due to the exclusion of more viable embryos with false positive test results than due to cryopreservation attrition, although with fewer clinical miscarriages and transfer procedures.

Table 8. Based on Rubio et al., 2017

Couples	100,000	Fresh + warmed embryo transfer strategy

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Live births	Clinical miscarriages	Transfers	First attempt live births	Live births	Clinical miscarriages	Transfers	First attempt live births
1	17,167	9,684	100,000	17,167	10,708	714	21,415	10,708
2	30,534	17,224	177,863	17,167	20,201	1,347	40,399	19,123
3	41,744	23,548	243,161	17,167	28,630	1,909	57,257	25,736
4	51,144	28,851	297,922	17,167	36,125	2,408	72,247	30,932
5	59,028	33,299	343,847	17,167	42,800	2,853	85,595	35,016
6	65,640	37,028	382,360	17,167	48,750	3,250	97,495	38,226
7	71,184	40,156	414,659	17,167	54,060	3,604	108,114	40,748
8	75,834	42,779	441,745	17,167	58,803	3,920	117,600	42,729
9	79,734	44,979	464,461	17,167	63,043	4,203	126,080	44,287
10	83,004	46,824	483,511	17,167	66,836	4,456	133,666	45,511

For 100,000 women with 5 morphologically transferable embryos (the average from the Rubio et al. 2017 trial report) and considering only up to one transfer attempt, the numbers of women with a live birth event are 35,016 with PGT-A and 17,167 without testing (difference 104.0%). Following a full cycle for 100,000 women there are 42,800 (42.8%) vs 59,028 (59.0%) live births (difference -27.5%). There are 2,853 vs 33,299 miscarriages (difference -91.4%) and 85,595 vs 343,847 transfers (difference -75.1%).

Given 5 embryos suitable for transfer or testing, approximately 1 in 3 women [100,000 / (33,299 – 2,853)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with a live birth of around 1 in 4 [59,028 / (59,028 – 42,800)].

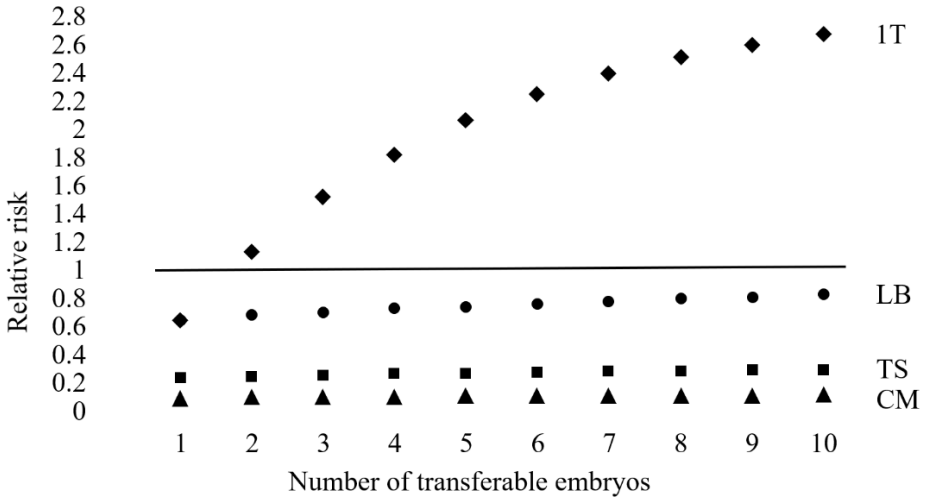

Fig.2. Based on Rubio et al., 2017. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Live birth event considering only up to 1 transfer attempt (1T). Live birth events (LB), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle.

Table 9. Based on Verpoest et al., 2018

Couples	100,000

Fresh + warmed embryo transfer strategy

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Live births	Clinical miscarriages	Transfers	First attempt live births	Live births	Clinical miscarriages	Transfers	First attempt live births
1	12,955	7,773	100,000	12,955	8,073	2,260	35,265	8,073
2	23,555	14,133	181,822	12,955	15,363	4,302	67,108	13,299
3	32,864	19,719	253,681	12,955	21,988	6,157	96,051	16,682
4	41,040	24,624	316,788	12,955	28,040	7,851	122,485	18,872
5	48,220	28,932	372,211	12,955	33,586	9,404	146,711	20,290
6	54,526	32,715	420,884	12,955	38,681	10,831	168,967	21,208
7	60,063	36,038	463,630	12,955	43,370	12,143	189,450	21,802
8	64,927	38,956	501,170	12,955	47,690	13,353	208,323	22,186
9	69,198	41,519	534,139	12,955	51,675	14,469	225,729	22,435
10	72,949	43,769	563,094	12,955	55,352	15,498	241,790	22,597

For 100,000 women with 4 morphologically transferable embryos (the average from the Verpoest et al. 2018 trial report) and considering only up to one transfer attempt, the numbers of women with a live birth event are 18,872 with PGT-A and 12,955 without testing (difference 45.7%). Following a full cycle for 100,000 women there are 28,040 (28.0%) vs 41,040 (41.0%) live births (difference -31.7%). There are 7,851 vs 24,624 miscarriages (difference -68.1%) and 122,485 vs 316,788 transfers (difference -61.3%).

Given 4 embryos suitable for transfer or testing, approximately 1 in 6 women [100,000 / (24,624 – 7,851)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with a live birth of around 1 in 3 [41,040 / (41,040 – 28,040)].

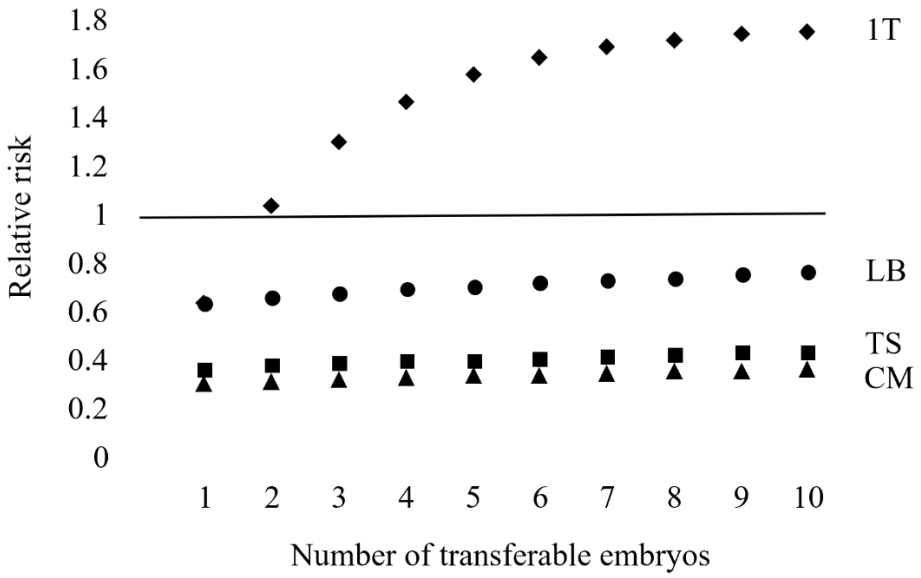

Fig.3. Based on Verpoest et al., 2018. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Live birth event considering only up to 1 transfer attempt (1T). Live birth events (LB), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle. Reproduced with permission from Scriven (2019).

3. Munné et al., 2019

The STAR trial (Munné et al., 2019 [NCT02268786]) was a multinational (north America, UK, Australia) multicentre (34 clinics and 9 testing laboratories) RCT for women aged 25-40 years undergoing IVF/ICSI with a least two blastocysts that could be biopsied. Ongoing clinical pregnancy at 20 weeks gestation rates (OPR) after single vitrified-warmed blastocyst transfer were compared following selection for euploidy using NGS-based PGT-A (Veriseq PGS, Illumina) or by morphology alone. The best intact embryo based on morphology was transferred in the control group, which may have introduced a positive bias. Women with no embryos with a euploid test result were excluded. Each clinic followed their own clinical and laboratory protocols and determined their own criteria for identifying aneuploid embryos, which were excluded from transfer. Embryos diagnosed to have mosaic, segmental or polyploid imbalance of uncertain clinical significance were not transferred, which may have introduced a negative bias.

The median age of the female partner was 34 years for both groups (range 25 – 40 y) with similar reasons for clinical infertility. The average number of day 5/6 blastocysts was 7 for both groups. A total of 661 women were randomised to PGT-A (n = 330) or morphology alone (n = 331). The ongoing pregnancy rate was similar for both groups per embryo transfer (50.0% [137/274] vs 45.7% [143/313]) and per intention to treat (41.8% [138/330] vs 43.5% [144/331]). The additional ongoing pregnancies in the intention to treat analysis are not explained but are like to be associated with the 7 women who withdrew from the PGT-A arm and the 14 women who withdrew from the control arm after randomisation. The clinical miscarriage rate was also evaluated and was estimated to be: PGT-A 16.4% (27/165) vs control 17.1% (30/175).

The following contingency tables were constructed:

Table 10.

Munné et al.		Embryo outcome		
Age: 25 - 40 y		OP +ve	OP -ve	Total
Test result	Normal	21668	21667	43335
	Abnormal	24019	32646	56665
	Total	45687	54313	100000

With a prevalence of non-viable morphologically transferable embryos of 54.3% (54,313 / 100,000), the likelihood of an abnormal test result correctly predicting no ongoing pregnancy was 57.6% (32,646 / 56,665) and the likelihood of a normal test result correctly predicting an ongoing pregnancy was 50.0% (21,668 / 43,335).

Table 11.

Munné et al.			
Age: 25 - 40 y	No test	PGT-A	RR
Embryos transfered	100000	43335	0.433
Ongoing clinical pregnancies	45687	21668	0.474
Per transfer	45.7%	50.0%	1.094

The PGT-A ongoing pregnancy rate per embryo transferred was superior (50.0% vs 45.7%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo; however, with 52.6% [(45,687 - 21,668) / 45,687) fewer ongoing pregnancies overall due to the exclusion of viable embryos with false positive test results.

Table 12. Based on Munné et al., 2019, 25 – 40 years

Couples	100,000	Freeze-all embryo transfer strategy

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Ongoing pregnancy	Clinical miscarriages	Transfers	First attempt ongoing preg.	Ongoing pregnancy	Clinical miscarriages	Transfers	First attempt ongoing preg.
1	42,946	8,885	94,000	42,946	20,368	3,985	40,735	20,368
2	67,448	13,955	147,631	45,523	36,587	7,159	73,173	32,439
3	81,428	16,847	178,230	45,677	49,503	9,686	99,004	39,593
4	89,404	18,498	195,688	45,686	59,788	11,698	119,574	43,833
5	93,954	19,439	205,648	45,687	67,979	13,301	135,954	46,345
6	96,551	19,976	211,331	45,687	74,501	14,577	148,998	47,835
7	98,032	20,283	214,573	45,687	79,694	15,593	159,385	48,717
8	98,877	20,458	216,423	45,687	83,830	16,402	167,657	49,240
9	99,359	20,557	217,478	45,687	87,124	17,046	174,243	49,550
10	99,635	20,614	218,081	45,687	89,746	17,560	179,488	49,734

For 100,000 women with 7 morphologically transferable embryos (the average from the study report for women undergoing transfer) and considering only up to 1 transfer attempt, the numbers of women with an ongoing pregnancy are 48,717 with PGT-A and 45,687 without testing (difference 6.6%). Following a full cycle for 100,000 women there are 79,694 (79.7%) vs 98,032 (98.0%) ongoing pregnancies (difference -18.7%). There are 15,593 vs 20,283 miscarriages (difference -23.1%) and 159,385 vs 214,573 transfers (difference -25.7%).

Given 7 embryos suitable for transfer or testing, approximately 1 in 21 women [100,000 / (20,283 – 15,593)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with an ongoing pregnancy of around 1 in 5 [98,032 / (98,032 – 79,694)].

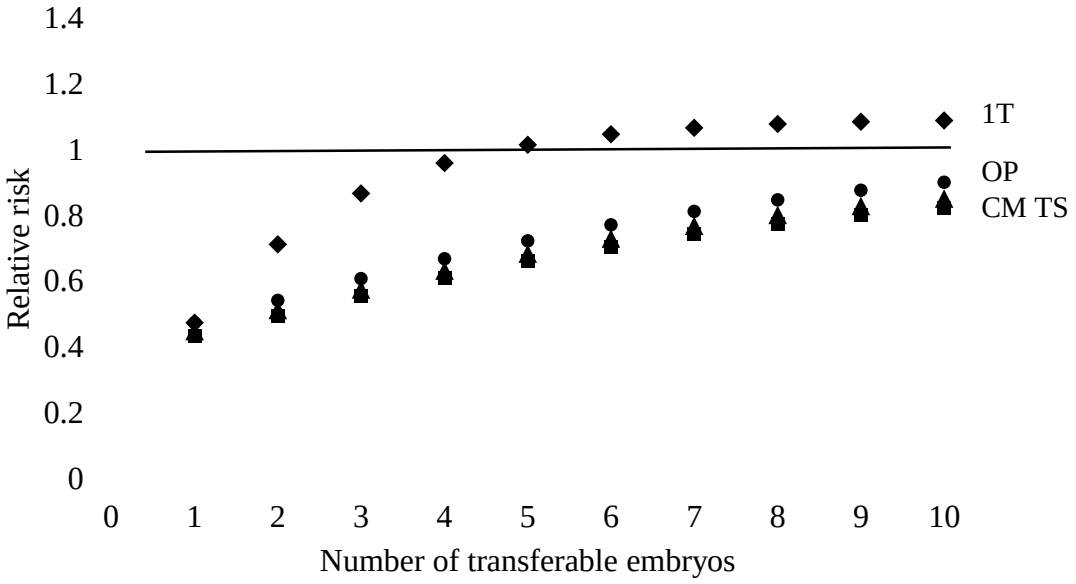

Fig.4. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Ongoing pregnancy considering only up to 1 transfer attempt (1T). Ongoing pregnancies (OP), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle.

The post hoc analysis of older women aged 35 to 40 years showed found a significant increase in the OPR per embryo transfer (50.8% [62/122] vs 37.2% [54/145]) but not per intention to treat. The probabilities for single embryo transfer were estimated as before. The clinical miscarriage rate was also evaluated and was estimated to be: PGT-A 13.7% (10/73) vs control 22.9% (16/70).

The following contingency tables were constructed:

Table 13.

Munné et al.		Embryo outcome		
Age: 35 - 40 y		OP +ve	OP -ve	Total
Test result	Normal	18530	17932	36462
	Abnormal	18711	44827	63538
	Total	37241	62759	100000

With a prevalence of non-viable morphologically transferable embryos of 62.8% (62,759 / 100,000), the likelihood of an abnormal test result correctly predicting no ongoing pregnancy was 70.6% (44,827 / 63,538) and the likelihood of a normal test result correctly predicting an ongoing pregnancy was 50.8% (18,530 / 36,462).

Table 14.

Munné et al.			
Age: 35 - 40 y	No test	PGT-A	RR
Embryos transfered	100000	36462	0.365
Ongoing clinical pregnancies	37241	18530	0.498
Per transfer	37.2%	50.8%	1.365

The PGT-A ongoing pregnancy rate per embryo transferred was superior (50.8% vs 37.2%) indicating that testing was more effective than a conventional morphological assessment alone to

select a viable embryo; however, with 50.2% [(37,241 - 18,530) / 37,241) fewer ongoing pregnancies overall due to the exclusion of viable embryos with false positive test results.

Table 15. Based on Munné et al., 2019, 35 – 40 years

Couples	100,000	Freeze-all embryo transfer strategy

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Ongoing pregnancy	Clinical miscarriages	Transfers	First attempt ongoing preg.	Ongoing pregnancy	Clinical miscarriages	Transfers	First attempt ongoing preg.
1	35,007	10,372	94,000	35,007	17,418	2,765	34,274	17,418
2	57,759	17,113	155,094	37,107	31,802	5,048	62,579	28,866
3	72,546	21,495	194,801	37,233	43,681	6,934	85,953	36,391
4	82,157	24,342	220,608	37,241	53,491	8,491	105,256	41,336
5	88,403	26,193	237,381	37,241	61,592	9,777	121,196	44,587
6	92,463	27,396	248,282	37,241	68,282	10,839	134,360	46,723
7	95,101	28,178	255,367	37,241	73,807	11,716	145,231	48,127
8	96,816	28,686	259,972	37,241	78,369	12,440	154,209	49,050
9	97,931	29,016	262,965	37,241	82,137	13,038	161,623	49,657
10	98,655	29,231	264,910	37,241	85,248	13,532	167,745	50,056

For 100,000 women with 5 morphologically transferable embryos (a likely average for this older age group) and considering only up to 1 transfer attempt, the numbers of women with an ongoing pregnancy are 44,587 with PGT-A and 37,241 without testing (difference 19.7%). Following a full cycle for 100,000 women there are 61,592 (61.6%) vs 88,403 (88.4%) ongoing pregnancies (difference -30.3%). There are 9,777 vs 26,193 miscarriages (difference -62.7%) and 121,196 vs 237,381 transfers (difference -48.9%).

Given 5 embryos suitable for transfer or testing, approximately 1 in 6 women [100,000 / (26,193 – 9,777)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with an ongoing pregnancy of around 1 in 3 [88,403 / (88,403 – 61,592)].

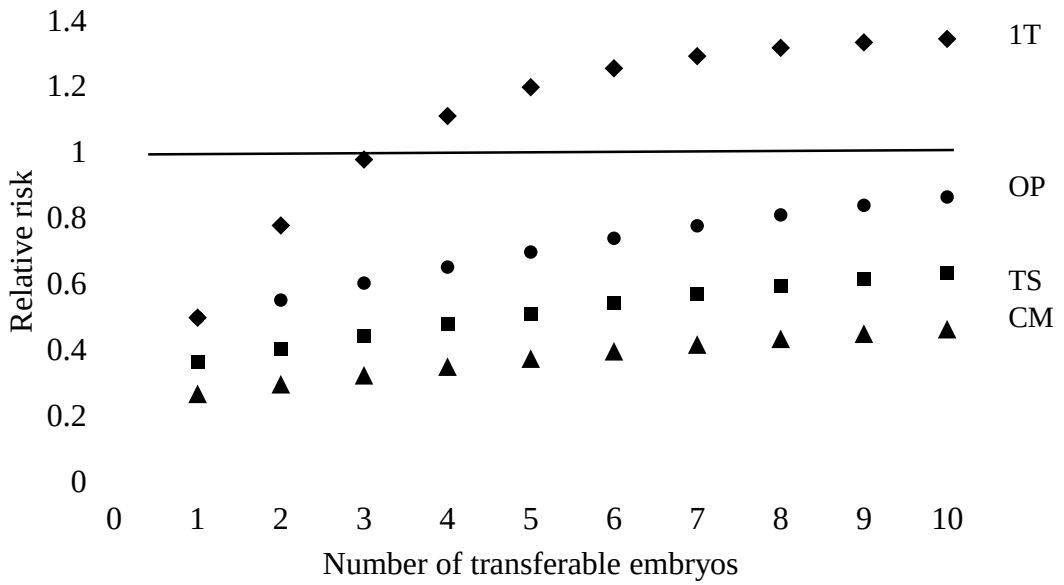

Fig.5. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Ongoing pregnancy considering only up to 1 transfer attempt (1T). Ongoing pregnancies (OP), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle.

4. Lee et al., 2017; 2019

A retrospective cohort study and cost-effectiveness analysis (Lee et al. 2017; 2019) considered the CLBR following up to three stimulated cycles. The decision of whether to use PGD- A or morphological assessment was made by the clinician in consultation with the patient. There was a higher number of oocytes collected on average in the PGD- A group than the control group (10.8 vs. 6.9) and more embryos available (4.4 vs. 2.6), suggesting a better prognosis for the women in the PGD- A group and the likely reason for the extra live birth effect observed (Table 18). The discontinue rate was substantial for both groups (71.8% vs 50.0%%). Testing was performed on single cells aspirated from day-3 embryos with six or more nucleated cells and less than 30% fragmentation using the Illumina 24Sure microarray system. Typically transfer occurred on day-2 for the control group and on day-5 or 6 for the tested group.

The following contingency tables were constructed:

Table 16.

Lee et al. 2017, 19		Embryo outcome		
Age: 37 - 45 y		LB +ve	LB -ve	Total
Test result	Normal	5550	13547	19097
	Abnormal	3558	77345	80903
	Total	9108	90892	100000

With a prevalence of non-viable embryos of 90.9% (90,892 / 100,000), the predictive value was estimated to be 95.6% (77,345 / 80,903) for an abnormal result and no live birth, and 29.1% (5,550 / 19,097) for a normal result and a live birth.

Table 17.

Lee et al. 2017, 19			
Age: 37 - 45 y	No test	PGT-A	RR
Embryos transferred	100000	19097	0.191
Live births	9108	5550	0.609
Per transfer	9.1%	29.1%	3.191

As before, the PGT-A live birth rate per embryo transferred was estimated to be superior (29.1% vs 9.1%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo; however, with 39.1% [(9,108 - 5,550) / 9,108) fewer live births overall due to the exclusion of viable embryos with false positive test results.

A before, a freeze-thaw survival rate of 94% was assumed for different numbers of available morphologically transferable embryos without testing. The clinical miscarriage rates for the control and study groups were estimated to be 33.8% (229/678) vs 20.9% (9/43). The results per 100,000 women and different numbers of morphologically transferable embryos in a first full cycle without dropout are summarised in Table 18.

Table 18. Based on Lee et al., 2017; 2019

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Live births	Clinical miscarriages	Transfers	First attempt live births	Live births	Clinical miscarriages	Transfers	First attempt live births
1	9,108	4,645	100,000	9,108	5,550	1,469	19,097	5,550
2	16,890	8,614	185,438	9,108	10,747	2,845	36,979	10,040
3	24,005	12,243	263,562	9,108	15,621	4,135	53,751	13,673
4	30,512	15,562	334,997	9,108	20,200	5,347	69,505	16,612
5	36,461	18,596	400,316	9,108	24,505	6,487	84,321	18,989
6	41,901	21,370	460,043	9,108	28,559	7,560	98,270	20,913
7	46,875	23,907	514,656	9,108	32,380	8,571	111,416	22,469
8	51,423	26,227	564,594	9,108	35,983	9,525	123,814	23,728
9	55,582	28,348	610,256	9,108	39,384	10,425	135,516	24,747
10	59,385	30,288	652,009	9,108	42,596	11,275	146,568	25,571

For 100,000 women with 3 morphologically transferable embryos and considering only up to one transfer attempt, the numbers of women with a live birth event are 13,673 with PGT-A and 9,108 without testing (difference 50.1%). Following a full cycle for 100,000 women there are 15,621 (15.6%) vs 24,005 (24.0%) live births (difference -34.9%). There are 4,135 vs 12,243 miscarriages (difference -66.2%) and 53,751 vs 263,562 transfers (difference -79.6%).

Given 3 embryos suitable for transfer or testing, approximately 1 in 12 women [100,000 / (12,243 – 4,135)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with a live birth of around 1 in 3 [24,005 / (24,005 – 15,621)].

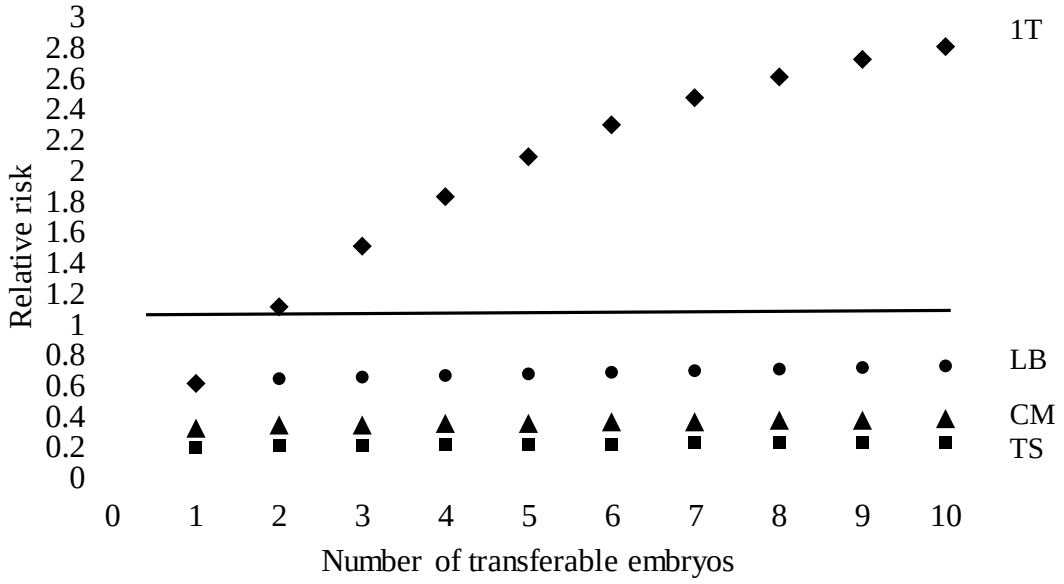

Fig.6. Based on Lee et al., 2017, 2019. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Live birth event considering only up to 1 transfer attempt (1T). Live birth events (LB), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle.

5. Sato et al., 2019

The recurrent pregnancy loss (RPL) study (Sato et al., 2019) included women aged 35 to 42 years with no previous live birth and 2 or more previous IVF-ET clinical miscarriages with at least 1 with aneuploidy. The median number of clinical miscarriages is likely to be 2 (around 56% of 41 women) with a range of 2 to 5. Testing for every chromosome was done at the blastocyst stage by trophectoderm biopsy and using aCGH (GenetiSure, Agilent). The live birth rates (LB) were 52.4% (11/21) and 21.6% (8/37) for the test and control groups respectively. The corresponding clinical miscarriage rates (CM) were 14.3% (2/14) and 18.2% (2/11) respectively.

Using the RPL results from the study, continency tables were constructed.

Table 19.

Sato et al.		Embryo outcome		
RPL Age: 35 - 42 y		LB +ve	LB -ve	Total
Test result	Normal	15291	13901	29192
	Abnormal	6330	64478	70808
	Total	21621	78379	100000

With 78.4% (78,379 / 100,000) prevalence of non-viable morphologically transferable embryos, the predictive value is estimated to be 91.1% (64,478 / 70,808) for an abnormal test result (and no live birth) and 52.4% (15,291 / 29,192) for an normal test result (and a live birth event).

Table 20.

Sato et al.			
RPL Age: 35 - 42 y	No test	PGT-A	RR
Embryos transfered	100000	29192	0.292
Live births	21622	15291	0.707
Per transfer	21.6%	52.4%	2.423

The PGT-A live birth rate per transfer is superior indicating that testing is more effective than a conventional morphological assessment alone to select a viable embryo; however, with 29.3% [(21,622 – 15,291) / 21,622] fewer live births following testing due to the exclusion from transfer of viable embryos with false positive test results.

Table 21. Based on Sato et al., 2019

	No genetic testing				Genetic testing for aneuploidy			
No. embryos	Live births	Clinical miscarriages	Transfers	First attempt live births	Live births	Clinical miscarriages	Transfers	First attempt live births
1	20,324	4,516	94,000	20,324	14,374	2,396	27,441	14,374
2	36,517	8,115	168,896	21,543	26,682	4,447	50,938	24,804
3	49,419	10,982	228,570	21,616	37,221	6,204	71,058	32,371
4	59,699	13,267	276,116	21,621	46,245	7,708	88,285	37,862
5	67,890	15,087	313,999	21,621	53,971	8,995	103,037	41,846
6	74,416	16,537	344,182	21,621	60,588	10,098	115,668	44,737
7	79,615	17,693	368,232	21,621	66,253	11,042	126,483	46,835
8	83,758	18,613	387,393	21,621	71,104	11,851	135,744	48,357
9	87,059	19,347	402,660	21,621	75,257	12,543	143,673	49,461
10	89,689	19,931	414,825	21,621	78,814	13,136	150,463	50,262

For 100,000 women with 4 morphologically transferable embryos (the likely average for the study) and considering only up to one transfer attempt, the numbers of women with a live birth event are 37,862 with PGT-A and 21,621 without testing (difference 75.1%). Following a full cycle for 100,000

women there are 46,245 (46.2%) vs 59,699 (59.7%) live births (difference -22.5%). There are 7,708 vs 13,267 miscarriages (difference -41.9%) and 88,285 vs 276,116 transfers (difference -68.0%).

Given 4 embryos suitable for transfer or testing, approximately 1 in 18 women [100,000 / (13,267 – 7,708)] are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with a live birth of around 1 in 6 [59,699 / (56,699 – 46,245)].

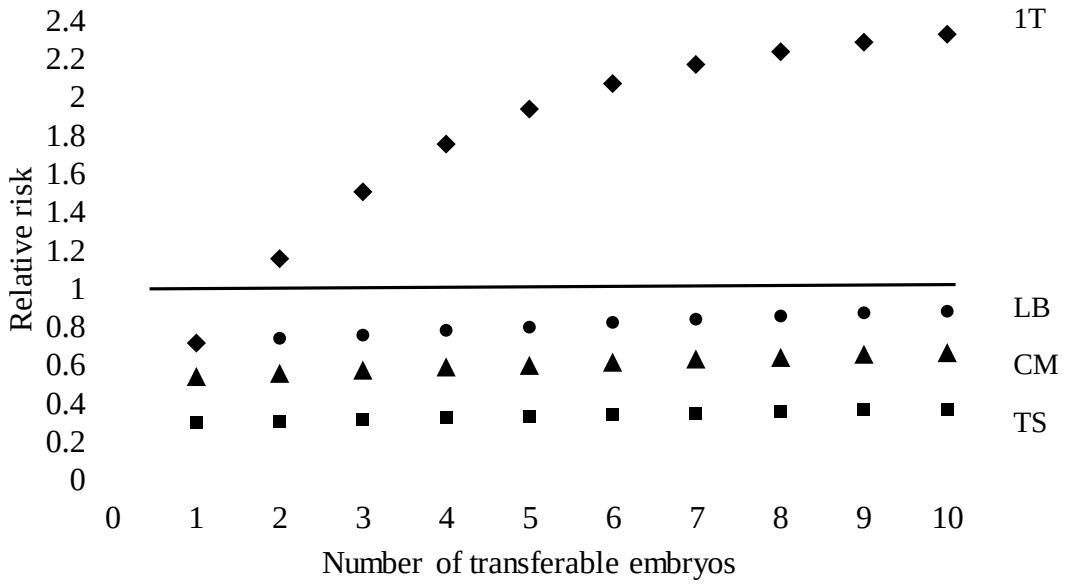

Fig.7. Based on Sato et al., 2019. The theoretical relative risk for PGT-A compared to a conventional embryo morphology assessment with single embryo transfer. Live birth event considering only up to 1 transfer attempt (1T). Live birth events (LB), clinical miscarriages (CM) and transfer procedures (TS) for a full cycle.

References

Lee E, Chambers GM, Hale L, Illingworth P, Wilton L. Assisted reproductive technology (ART) cumulative live birth rates following preimplantation genetic diagnosis for aneuploidy (PGD- A) or morphological assessment of embryos: A cohort analysis. Aust N Z J Obstet Gynaecol. 2017; 58: 525–532. https://doi.org/10.1111/ajo.12756

Lee E, Costello MF, Botha WC, Illingworth P, Chambers GM. A cost-effectiveness analysis of preimplantation genetic testing for aneuploidy (PGT-A) for up to three complete assisted reproductive technology cycles in women of advanced maternal age. Aust N Z J Obstet Gynaecol. 2019; 59: 573-579. https://doi.org/10.1111/ajo.12988

Munné S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, et al.; STAR Study Group. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril. 2019; 112: 1071-1079. https://doi.org/10.1016/j.fertnstert.2019.07.1346

Rubio C, Bellver J, Rodrigo L, Castillón G, Guillén A, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. Fertil Steril. 2017; 107: 1122-1129. https://doi.org/10.1016/j.fertnstert.2017.03.011

Sato T, Sugiura-Ogasawara M, Ozawa F, Yamamoto T, Kato T, et al. Preimplantation genetic testing for aneuploidy: a comparison of live birth rates in patients with recurrent pregnancy loss due to embryonic aneuploidy or recurrent implantation failure. Hum Reprod. 2019; 34; 2340-2348. https://doi.org/10.1093/humrep/dez229

Scriven PN. Towards a better understanding of preimplantation genetic screening and cumulative reproductive outcome: transfer strategy, diagnostic accuracy and cost-effectiveness. AIMS Genetics. 2016; 3: 177-195. http://dx.doi.org/10.3934/genet.2016.3.177

Scriven PN. The usefulness of preimplantation genetic testing for chromosome aneuploidy informed by a randomised controlled trial. OBM Genetics. 2019; 3: 6. http://dx.doi.org/10.21926/obm.genet.1901061

Verpoest W, Staessen C, Bossuyt PM, Goossens V, Altarescu G, et al. Preimplantation genetic testing for aneuploidy by microarray analysis of polar bodies in advanced maternal age: a randomized clinical trial. Hum Reprod. 2018; 33: 1767-1776. https://doi.org/10.1093/humrep/dey262

Yang Z, Liu J, Collins GS, Salem SA, Liu X, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. Mol Cytogenet. 2012; 5: 24. https://doi.org/10.1186/1755-8166-5-24

Appendix – Calculating Probabilities

Probabilities for single embryo transfer estimated from study reports (Scriven, 2016; Scriven, 2019)

A – proportion of embryos with an aneuploid result in the test group

B – proportion of all embryos transferred in the test group (single and dual embryo transfer, fresh and frozen) that resulted in live born offspring (or an ongoing pregnancy)

C- proportion of all embryos transferred in the untested group that resulted in live born offspring (or an ongoing pregnancy)

D – proportion of test results that are true normal (live born/ongoing and an euploid test result)

= (1 – A) x B

E – proportion of test results that are false normal (no live birth/ongoing and an euploid test result)

= 1 – A – D

F – proportion of test results that are false abnormal (live born/ongoing and an euploid test result)

= C – D

G – proportion of test results that are true abnormal (no live birth/ongoing and an aneuploid test result)

= A – F

H – prevalence of non-viable transferable embryos

= E + G

I – positive predictive value (the proportion of abnormal test results that correctly predict no live birth/ongoing pregnancy

= G / A

J – negative predictive value (the proportion of normal test results that correctly predict a live birth/ongoing pregnancy, and the likelihood of a live birth/ongoing pregnancy for a single embryo transferred with a normal test result

= D / (1 – A)

K – the likelihood of a live birth/ongoing pregnancy for a single embryo transferred without testing

= D + F

L – the proportion of viable embryos excluded due to an incorrect test result

= F / (D + F)

The likelihood of a clinical miscarriage was estimated from the number of gestational sacs that did not result in a live born offspring/ongoing pregnancy, with and without testing

The freeze-thaw survival rate was assumed to be 94%